REMARKS

Reconsideration and allowance are respectfully requested.

Claims 22-24, 26-33, 35-38 and 40-51 are pending. Rejoinder of the withdrawn claims is requested upon an indication that a generic claim is allowable.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 22-24, 26-28, 42 and 50 were rejected under Section 112, first paragraph, because the specification "does not reasonably provide enablement for any other two-cell complex between any other pathogenic target and any other receptor in contact with any other binding agent." Applicant traverses.

Bacteria may use their target receptors such as adhesins, fibrillae, and fimbriae or pillin to bind recognition regions of the host (e.g., cell-surface proteins or sugars of the host). See Table 2 (columns headed "Adhesin" and "Receptor", respectively) of Todar's Online *Textbook of Bacteriology*; a copy of which is attached. A review of viral mechanisms of entry into host cells shows that the identities of target receptors and their host recognition regions are known for at least alpha herpes virus, influenza virus, herpes simplex virus 1, Epstein-Barr virus, Newcastle disease virus, adenovirus, adeno-associated virus, dengue virus, tick-borne encephalitis virus, papilloma virus, paramyxo-virus 3, and Sindbis virus, human cytomegalovirus, hepatitis C virus, and Ebola virus. See pages 237-238 of Smith & Helenius *Science* 304:237-239 (2004); a copy of which is attached. Finally, binding agents are well known in the prior art as shown by looking at any general reference on cross-linking agents. See, for example, pages 173-214 of 1999-2000 *Pierce Catalog*; a copy of which is enclosed.

Using such target receptors, recognition regions, and binding agents which are known, a person skilled in the art would not require undue experimentation to practice the claimed invention in accordance with Applicant's teachings in his specification. It is not required that the specification teach what is known in the art. Moreover, given this great amount of knowledge and the high level of skill that are available in the art, the scope that is enabled by Applicant's disclosure is commensurately broad. The disclosure of every possible combination of two-cell complexes (or forming complexes with every possible binding agent) is not, and should not be, required to satisfy the requirements of Section 112.

Claims 41 and 51 were rejected under Section 112, first paragraph, because the specification "does not reasonably provide enablement for any neutralizing antibody." Applicant traverses.

A neutralizing antibody is understood by persons skilled in the art to refer to an antibody which at least binds to and "neutralizes" virus infectivity under defined conditions in vitro. See Reading & Dimmock *Arch. Virol.* 152:1047-1059 (2007). Neutralization by an antibody can act through different mechanisms: e.g., aggregating virions, destabilizing the virion's structure, inhibiting virion attachment to target cells, inhibiting the fusion of the virion lipid membrane with the membrane of the host cell, inhibiting entry of a non-enveloped virus' genome into the cell cytoplasm, inhibiting a function of the virion core through a signal transduced by the antibody, transcytosing IgA, and binding to nascent virions to block their budding or release from the cell surface. Id. Therefore, the multiple mechanisms of antibody neutralization do not require they cause cytotoxicity (cf. Nunberg) and confirming the ability to neutralize virus infectivity does not require undue experimentation (cf. Lee). Reading & Dimmock state, "The mechanism of neutralization is determined by the properties of both a virion epitope and the antibody that reacts with it. Further, since a virus has at least several unique epitopes sited in different locations on the virion, and since the paratope and other properties of the reacting antibody can vary, this means that a virus can be neutralized by <u>several</u> different mechanisms" (emphasis added).

A person skilled in the art would not have found it difficult or unpredictable to generate antibodies to the two-cell complexes of the invention and to confirm they are neutralizing according to the teachings of Applicant's specification. No reasoning or evidence of record in this application contradicts those teachings. Certainly neutralizing antibodies with the properties required by Applicant's claims exist. See Hernandez et al. *J. Virol.* 82:5750-5760 (2008). The enclosed article relates to a different virus from the virus used in Applicant's examples (i.e., Sindbis virus) showing that the invention is not limited to a specific pathogen. Hernandez's neutralizing antibody recognizes a conformational change in the viral e1 glycoprotein and a loss of infectivity is correlated with inducing that change by antibody binding. Thus, the Examiner's allegation that undue experimentation would be required to practice the claimed invention with a neutralizing antibody is contradicted.

Withdrawal of the enablement rejections made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). A specification need not teach, and preferably omits, what is well known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Claims 22-24, 26-28, 41-42 and 50 were rejected under Section 112, first paragraph, as allegedly "failing to comply with the written description requirement." Applicant traverses because the specification teaches a representative number of species within the claimed genus or such species would have been known to a person skilled in the art as of the effective filing date.

The Examiner objects that the genuses of binding agents, target receptors, and regions of the infectious pathogenic agent recognizing the target receptors are not supported by a representative number of species. A specification need not teach, and preferably omits, what is well known in the art. *Hybritech*, 231 USPQ at 94. Therefore, species known in the prior art as belonging to the claimed genus also must be considered in determining whether the written description requirement is satisfied.

As admitted on page 10 of the Office Action, target receptors including MBP receptor, dextran receptor, lectin receptor, integrins, heparin sulfate proteoglycans, and other cell surface receptors (e.g., CD4, CCR5) were known in the art. They have a diversity of chemical structures and biological functions to support the broad genus of target receptors. Similarly, the broad genus of regions that the receptors recognize are known to persons skilled in the art. They include viral glycoproteins and other cellular molecules of bacteria and parasites, which also have a diversity of chemical structures and biological functions, that are used by the pathogen to attach and invade the host cell. Also see the enclosed Table 2 of Todar's Online *Textbook of Bacteriology* and the enclosed pages 237-238 of Smith & Helenius. Binding agents are also well known in the prior art as shown by looking at any general reference on cross-linking agents. See, for example, pages 173-214 of 1999-2000 *Pierce Catalog*; a copy of which is enclosed.

Persons skilled in the art would conclude that the claimed genuses of binding agents, target receptors, and recognition regions are supported by a representative number of species. Therefore, the written description requirement is satisfied.

Withdrawal of the written description rejection made under Section 112, first pararaph, is requested because the specification conveys to a person skilled in the art that Applicant was in possession of the claimed invention as of the filing date.

35 U.S.C. 102 – Novelty

A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosure cited as prior art is not enabled. *Amgen v. Hoechst Marion Roussel*, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003); See *Bristol-Myers Squibb v. Ben Venue Laboratories*, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the [prior

art] reference must also enable one of skill in the art to make and use the claimed invention"). The prior art reference must sufficiently describe the claimed invention to have placed the public in possession of it; such possession is effected if one of ordinary skill in the art could have combined the prior art's description of the invention with his own knowledge to make the claimed invention. *Elan Pharms. v. Mayo Found.*, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003); *In re Donohue*, 226 USPQ 619, 621 (Fed. Cir. 1985).

Claims 22-24, 26-33, 35-37, 41-42, 44 and 50-51 were rejected under Section 102(b) as allegedly anticipated by LaCasse et al. (*Science* 283:357-362, 1999). Applicant traverses since the cited reference's conclusion that serum raised against their immunogen contains neutralizing antibodies was subsequently retracted by the senior author (see Nunberg's letter in *Science* 296:1025, 2002; a copy of which is of record in this application).

The LaCasse et al. reference was cited in the Action, but it appears that the Examiner was not aware of the retraction of their "published results" after "a specific cytotoxic effect" was discovered in the sera elicited after immunization. The contribution of antibodies against the immunogen was not measured (e.g., "This unappreciated cytotoxicity significantly reduces both the potency and the breadth of primary virus neutralization"). Nunberg admitted, "The basis for the specific cytotoxic effect is unknown" in his letter. Since the origin of this artifact was not explained and the skilled artisan would not have been able to eliminate it based on the evidence of record, undue experimentation would have been required to practice what was disclosed in the cited reference. Thus, the public was <u>not</u> put in possession of the claimed invention by LaCasse et al.

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 41 and 51 were rejected under Section 102(b) as allegedly anticipated by Thali et al. (*J. Virol.* 67:3978-3988, 1993). Applicant traverses.

Thali's antibody was found in viral infected humans who do not appear to have been immunized with a cellular complex of target receptor and recognition region. By contrast, Applicant's claimed invention requires immunization with the cellular complex. Further, to the extent that Thali discloses a neutralizing antibody, it is another example contradicting the Examiner's allegations above with respect to neutralizing antibodies not being enabled to make and use Applicant's claimed invention.

Therefore, the cited reference does anticipate the claimed invention.

Claims 41 and 51 were rejected under Section 102(b) as allegedly anticipated by Lee et al. (*J. Virol.* 71:6037-6043, 1997). Applicant traverses.

Lee's antibody was raised against a protein complex of soluble CD4-gp120 (IIIB). By contrast, Applicant's claimed invention requires immunization with a cellular complex (i.e., cell-bound target receptor and recognition region complexes instead of soluble complexes). Further, Lee's monoclonal antibody CG10 enhanced cell fusion, which is not a requirement of Applicant's claims 41 and 51.

Therefore, the cited reference does anticipate the claimed invention.

Withdrawal of the Section 102 rejections is requested because the cited prior art references fail to enable the claimed invention or to disclose all limitations of the claims.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the back-ground knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning

is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning"). Thus, an obviousness rejection requires "some rationale, articulation, or reasoned basis to explain why the conclusion of [prima facie] obviousness is correct." *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396.

Claims 22 and 40 were rejected under Section 103(a) as allegedly unpatentable over LaCasse et al. (*Science* 283:357-362, 1999) in view of Rossio et al. (*J. Virol.* 72: 7992-8001, 1998). Applicant traverses.

The failure of LaCasse et al. to disclose the claimed invention is not remedied by the attempt to combine that disclosure with Rossio et al. As noted above, the LaCasse et al. reference is not enabled for the disclosure relied upon by the Examiner. Applicant submits that this defect in the obviousness rejection is sufficient to establish patentability over the cited references so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Claims 22-24, 26-33, 35-38 and 40-41 were rejected under Section 103(a) as allegedly unpatentable over LaCasse et al. (*Science* 283:357-362, 1999) in view of Riley et al. (*J. Virol.* 72:8273-8280, 1998). Applicant traverses.

The failure of LaCasse et al. to disclose the claimed invention is not remedied by the attempt to combine that disclosure with Riley et al. As noted above, the LaCasse et al. reference is not enabled for the disclosure relied upon by the Examiner. Applicant submits that this defect in the obviousness rejection is sufficient to establish patentability over the cited references so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Claims 24, 43-44 and 47 were rejected under Section 103(a) as allegedly unpatentable over LaCasse et al. (Science, 283:357-362, 1999) in view of Murphy et al. (Genet. Anal. Tech. Appln., 7:160-171, 1990). Applicant traverses.

The failure of LaCasse et al. to disclose the claimed invention is not remedied by the attempt to combine that disclosure with Murphy et al. As noted above, the LaCasse et al. reference is not enabled for the disclosure relied upon by the Examiner. Applicant submits that this defect in the obviousness rejection is sufficient to establish patentabi-

lity over the cited references so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Withdrawal of the Section 103 rejections is requested because the cited prior art references fail to render obvious the claimed invention.

Conclusion

Having fully responded to the pending Office Action, Applicant submits that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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